

# Physical Urticaria

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**Abstract** The physical urticarias are a heterogeneous subgroup of chronic urticarias in which wheals can be reproducibly induced by different specific physical stimuli such as cold, heat, pressure, vibration, or sunlight. Physical urticarias comprise up to 25 % of chronic urticarias and occur more frequently in young adults. Symptoms, i.e. wheal and flare responses or angioedema, are usually limited to the skin areas exposed to the eliciting stimulus. However, generalised urticaria with variable extracutaneous manifestations can also occur. Some patients may also present with more than one physical urticaria. Skin lesions in physical urticaria result from mast cell activation and mediator release. The mechanisms by which physical stimuli activate skin mast cells are not fully understood. Because of this, trigger avoidance and symptomatic treatment are key therapeutic concepts for physical urticarias. Identification of the inducing physical trigger, including its individual thresholds, is necessary for an effective therapy. Here, we have summarized clinical features, diagnostic workup and therapy options for physical urticarias.

**Keywords** Physical urticaria · Urticaria factitia · Symptomatic dermatographism · Delayed pressure urticaria ·

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Cold contact urticaria · Heat contact urticaria · Solar urticaria · Vibratory urticaria/angioedema · Angioedema

## Introduction

Physical urticaria is a group of acquired diseases characterized by a common and distinctive clinical pattern, i.e. the induced development of itchy wheal and flare type skin lesions and/or angioedema. These symptoms are induced by exogenous physical triggers specific to the physical urticaria subtype: mechanic (friction, pressure and vibration), thermal (cold and heat), and electromagnetic (solar) radiation (Table 1). In all physical urticarias, skin sites of trigger exposure can react with wheals and angioedema, with the exception of urticaria factitia (where only wheals are found and angioedema is absent) and pressure urticaria (with only angioedema but no wheals).

Little is known about the prevalence of physical urticarias. Up to 0.5 % of the population is thought to suffer from chronic physical urticaria, and these conditions comprise up to 15–25 % of chronic urticarias [1]. Physical urticarias often occur in combination with other forms of chronic urticaria, e.g. spontaneous urticaria and/or another subtype of inducible urticaria [2]. The underlying causes of physical urticaria remain unknown. They are diagnosed on the basis of patients' case histories and on the results of skin provocation testing. Patients who are suspected of having physical urticaria should be tested for every potentially relevant trigger [3•]. Since patients display a large range of individual trigger thresholds, which may vary with time and therapy, trigger thresholds should be determined in each patient who is diagnosed with physical urticaria, and must be repeated thereafter. This helps patients to prevent symptoms in daily life, and helps treating physicians to optimize the

**Table 1** Subtypes of physical urticaria

Subtypes of physical urticaria		
Type of Stimuli	Form of Urticaria	Relevant trigger
Mechanic	Urticaria factitia	Friction, rubbing
	Delayed pressure urticaria	Static pressure
	Vibratory urticaria/ angiooedema	Vibration
Thermal	Cold contact urticaria	Cold contact
	Heat contact urticaria	Heat contact
Electromagnetic waves	Solar urticaria	UV-/visible Light

therapy. The goal of therapy is the absence of symptoms. This is achieved primarily by the avoidance of relevant stimuli and the use of drugs that inhibit the effects of mast cell mediators, such as histamine. Second-generation non-sedating antihistamines are recommended as a first-line symptomatic treatment [4•]. In most patients, higher than standard dosing is required to prevent the symptoms.

The aim of this review is to discuss the current diagnostic and therapeutic possibilities for each form of physical urticaria.

### Urticaria Factitia

Urticaria factitia (UF) (syn. symptomatic dermographism, dermographic urticaria) is the most common subtype of physical urticaria [2, 5, 6]. UF mainly affects young adults, and the mean duration of the disease is 6.5 years [7]. UF is characterized by the development of itchy wheals induced by mild stroking, rubbing or scratching of the skin at the site of exposure to this stimulus. Typically, whealing occurs within seconds to minutes after skin provocation and lasts for half an hour to two hours [3•]. UF should be suspected in patients with a suggestive history and then confirmed by a positive skin provocation test. Skin provocation tests for UF are done by rubbing the skin of the upper back or the volar of the forearm lightly with a smooth blunt object (i.e. the tip of a wooden spatula), or by using a purpose-built instrument (dermographometer). Skin responses are assessed 10 minutes after provocation. As recommended by current guidelines, skin tests in UF patients should include threshold testing, for which a dermographometer is required (Fig. 1). Trigger levels of up 100 g/mm<sup>2</sup> should be used to determine the minimal shear force that is sufficient to induce whealing (i.e. the trigger threshold). Threshold assessments can help to monitor disease activity over time, and to determine patients' responses to treatment. The underlying causes of UF are unknown. Various drugs (e.g. progesterone, atorvastatin), as well as infections (e.g. hepatitis, dental infections, upper

respiratory tract infections), and other conditions (e.g. diabetes mellitus), have been claimed to be responsible for UF [8, 9], but evidence for this is circumstantial, and controlled studies are missing and should be performed.

UF treatment is, therefore, based on symptomatic therapy and symptom avoidance. Some patients can prevent, or at least reduce, whealing by measures that decrease mechanical irritation of the skin, such as avoiding the vigorous use of a towel after showering, or choosing light and non-irritating clothing. For symptomatic UF treatment, non-sedating second-generation H1-antihistamines are recommended as first-line treatment [10]. Patients who do not respond to standard doses may benefit from higher doses, i.e. up to fourfold, and, if needed, the additional use of leukotriene antagonists and/or H2-antihistamines, although evidence from controlled trials is presently missing. Other second line treatments described to be effective are ciclosporin A [11•], omalizumab [12•], and narrow-band UV-B [13•], but evidence for this is anecdotal and controlled trials need to be performed.



**Fig. 1** Urticaria factitia – threshold testing by using a combined dermographometer with the force levels of up 100 g/mm<sup>2</sup>

## Delayed Pressure Urticaria

Delayed pressure urticaria (DPU) is characterized by the development of erythematous skin swellings, i.e. angioedema, at sites of exposure to sustained pressure to the skin, usually with a few hours (6–8 h) delay [3•, 14]. In contrast to most other physical urticarias, the skin symptoms in DPU are frequently associated with severe burning and pain, and systemic problems such as flu-like symptoms, malaise, and arthralgia, which can result in severe quality of life impairment and physical disability. These differences suggest that mast cell mediators such as proinflammatory cytokines, e.g. IL-1, IL-3, IL-6, tumor necrosis factor, and platelet factor 4 or beta-thromboglobulin, in addition to histamine, may be involved in the pathogenesis of DPU. DPU patients have been described as developing swellings of the upper airways (after endotracheal intubation) and the gastrointestinal tract (after esophagogastroduodenoscopy) [12•].

When DPU is suspected from a patient's history, skin provocation tests should be performed. This should be done by applying pressure to the skin using weighted rods or a dermatographometer. The recommended sites for standard diagnostic testing of DPU are the shoulder, upper back, thighs, or the volar surface of the forearm. Weighted rods (5 kg with 6.5 cm diameter or, 2.5 kg with 1.5 cm diameter) are applied for 15 minutes and the dermatographometer (set at 100 g/mm<sup>2</sup>) is applied for 70 seconds induction. Test reactions are considered to be positive if a red palpable swelling is seen 6 hours after examination.

Provocation test-positive patients should be subjected to threshold testing which can be done using weighted rods (6.5 cm diameter) with weights of 1 to 5 kg for 15 minutes; the dermatographometer (100 g/mm<sup>2</sup>) is used from 20 up to 60 seconds [3•, 14].

The underlying causes of DPU are unknown. Symptom prevention and symptomatic treatment are the cornerstones of DPU management. Swelling frequency and/or severity can be reduced by non-sedating H1-antihistamines, usually requiring higher than standard dosing [4•, 5, 14]. Alternative or additional interventions are required in many DPU, but the evidence in support of their use is of low or very low quality. For example, combinations of drugs such as montelukast with non-sedating H1-antihistamines (desloratadine) have been successfully used in some cases [4•, 15]. Monotherapy of DPU with dapson or sulfasalazine can reportedly also result in a good therapeutic benefit in some patients [5, 7, 16•]. Short-term oral corticosteroids are reserved for very severe and recalcitrant DPU, because of the risk of severe side effects [7, 14]. Successful treatment of DPU with omalizumab, a recombinant antibody against IgE, remains an experimental therapy option and requires further investigation of efficacy and safety [17•].

## Cold Contact Urticaria

Cold contact urticaria (CCU) (syn. acquired cold urticaria) is a common form of physical urticaria, characterized by the development of wheal and flare-type skin reactions or angioedema due to the release of histamine and other proinflammatory mast cell mediators after skin exposure to cold. Typically, symptoms occur within a few minutes after cold contact (cold air, liquids or objects), and are limited to cold-exposed skin areas. However, extensive cold contact (e.g. swimming in cold water) may lead to systemic reactions including shock [18]. Several cases of death due to anaphylaxis while swimming in cold water have been reported [19]. Up to 72 % of CCU patients experience at least one systemic reaction after extensive cold contact [18–21]. Besides aquatic activities, patients should avoid ice-cold drinks and food, in order to prevent oropharyngeal oedema. CCU may occur at any age, but shows a peak in young adults and a weak predominance in women [18, 20, 22]. The mean duration of CCU is held to range from 4.8 to 7.9 years [18, 20, 22]. Among the different subtypes, the frequency of CCU is reported to vary between 6 % and 34 % [21, 23].

Rare forms of atypical CCU include delayed CCU, where localized whealing appears 12–48 h after cold exposure; cold dependent dermatographism, which is limited to cold-exposed and mechanically stimulated skin; and cold-induced cholinergic urticaria, which occurs after physical exercises in cold environments [21]. Cold-induced whealing is also seen in some very rare hereditary (autosomal-dominant) autoinflammatory conditions, such as familial cold auto-inflammatory syndrome (FCAS). In these conditions, wheals usually occur 1–2 h after systemic exposure to cold, but they cannot be induced by localized cold provocation of the skin. Here, activation of NLRP3 inflammasome complex due to mutation of CIAS1/NLRP3 induces the release of interleukin-1 $\beta$  from mast cells [24]. The pathogenetic relevance of interleukin-1 $\beta$  in these hereditary diseases is demonstrated by a quick and excellent response of symptoms to interleukin-1 antagonists [25].

CCU symptoms are induced by histamine and other inflammatory mediators released from skin mast cells such as prostaglandin D<sub>2</sub>, platelet-activating factor and leukotrienes [26]. The mechanisms of cold-induced activation of mast cells still remain unknown. Up to 40 % of CCU patients exhibit antibodies against IgE or against the high-affinity receptor for IgE [27], but the role and relevance of these antibodies in CCU still must be identified. Mast cell activation has been postulated to involve IgE-binding of cold-dependent skin antigens, since CCU can be adoptively transferred to healthy individuals by intracutaneous injection of the serum of some CCU patients [28].

Patients who report cold-induced whealing or angioedema should be subjected to cold stimulation testing by placing a melting ice cube in a thin plastic bag (to avoid cold damage of the skin) on the volar forearm for 5 minutes [29]. The test response should be assessed 10 minutes after removing the ice cube. It is considered positive if the test site shows a palpable and clearly visible wheal, which is usually associated with a pruritic or burning sensation. A positive ice cube test confirms CCU and should prompt further tests to determine individual temperature and/or stimulation time thresholds [3]. For this purpose, a Peltier element-based electronic provocation device (TempTest®, emo systems GmbH, Berlin, Germany) has been developed, which allows simultaneous skin exposure to 12 different temperatures from 4°C to 42°C in a standardized and reproducible way [30]. Critical temperature threshold tests enable patients to better avoid situations that cause whealing. They also show how effectively patients are protected by therapy, and allow individualized treatment optimization [31•]. Laboratory tests are of limited value in most cases of cold urticaria [32]. Since many patients show critical temperature thresholds of 20°C and higher, the avoidance of below-threshold temperatures is difficult in daily life, especially in countries with cold climates. Nevertheless, patients should be warned to avoid skin contact with subthreshold temperatures. In patients with impaired quality of life or a risk of severe reactions, and who cannot prevent symptoms by cold avoidance, additional therapeutic measures are required [33].

The treatment of choice in CCU patients is the preventive use of non-sedating H1-antihistamines. These drugs have been shown to be effective, safe and well tolerated in several controlled studies [34]. They are recommended by the current EAACI/GA<sup>2</sup>LEN/EDF/WAO guidelines as first line therapy [4•, 34]. In many cases, however, conventional doses do not completely protect patients from cold-induced symptoms. Recently, two independent studies have shown that higher-than-standard doses of a non-sedating H1-antihistamine are significantly more effective than the standard-dosed treatment [35–37, 38•]. Treatment options reported for antihistamine-resistant CCU include Omalizumab (anti-IgE), Etanercept (anti-tumor necrosis factor) and Anakinra (anti-interleukin 1), but controlled studies are missing [12•, 39, 40•, 41•]. Symptoms can also be prevented by the induction and maintenance of tolerance to subthreshold temperatures, which requires supervision and guidance by the treating physician because of the risk of systemic anaphylactic reactions. Cold tolerance induction is achieved by gradually and carefully decreasing of the temperature of showers, starting with above-threshold temperatures, and tolerance is maintained by daily cold showers [42, 43].

## Heat Contact Urticaria

Heat contact urticaria (HCU) is a rare physical urticaria, which is characterized by the appearance of urticarial lesions after contact with temperatures that exceed those of the skin [44]. Less than 100 cases of localized heat urticaria have been reported in the literature, including cases in children and familial heat urticaria [45].

Whealing typically develops within a few minutes after heat exposure, and it resolves after 1–3 h. For provocation testing, heat should be applied for 5 minutes (metal/glass cylinders filled with hot water, hot water bath, TempTest®) at a temperature of 45°C. In patients with a positive response, stimulation temperature and stimulation time threshold should be determined [3•].

Treatment options for localized heat urticaria are limited. Antihistamines are the first choice for symptomatic therapy [4•]. In difficult-to-treat patients, omalizumab can be effective [12•, 46].

## Solar Urticaria

Solar urticaria (SU) is characterized by whealing of the skin exposed to visible or ultraviolet (UV) light. SU occurs at any age, but young adults and women are affected more frequently [47, 48]. Urticarial lesions develop within 5–10 minutes of sun exposure and are limited to exposed areas. Systemic symptoms such as wheezing, syncope, and even anaphylaxis may occur when a large body area is exposed to sunlight [49]. There are also a number of other clinical manifestations of SU described in literature, including cases of delayed onset of whealing, as well as fixed SU, or erythema with itching but without wheals [50–52]. Bruised skin seems more sensitive to develop symptoms of SU. A possible cause for this could be the migration of photoallergens into the skin through damaged vessels [53, 54].

The diagnosis of SU is based on a detailed history and provocation testing. Solar simulators or monochromators should be used for this purpose. Provocation testing should be on body areas that are usually not exposed to sunlight, e.g. buttocks, using UVA, UVB and visible light separately. In patients with a positive test reaction (wheal and flare 5–10 min after end of provocation) threshold testing should be performed using incremental radiation doses [3•].

Management of SU is challenging both for physicians and patients, because exposure to sunlight is hard to avoid, and because many patients fail to experience complete protection from symptoms by non-sedating antihistamines, which are recommended as first line treatment [4•]. Only one of three patients is reported to show a good response [47, 48]. Repeated exposure to sunlight may induce tolerance, and UVA, broadband UVB, and narrowband UVB irradiation have been used for the treatment of SU [55, 56]. Anti-IgE therapy has been



reported to be effective in certain patients [12•, 57–59]. There are also different reports on the efficacy of intravenous immunoglobulin treatment in SU [60–62]. Recently, symptoms were reported to be reduced in SU patients treated with afamelanotide, a potent  $\alpha$ -melanocyte stimulating hormone analogue. The latter increases melanisation of the skin, and thus protects it from penetration of UV–visible wavelengths [63•].

## Vibratory Angioedema

Vibratory angioedema/urticaria (VA) is a rare physical urticaria defined by the presence of skin swellings and itching after exposure to vibration at the contact site [64]. VA is confirmed by cutaneous swelling 10 minutes after provocation testing using a laboratory vortex mixer [3•]. Non-sedating antihistamines are the first line treatment.

## Conclusions

Physical urticaria is a group of usually chronic, inducible urticarial conditions, characterized by wheals and/or angioedema that only occur in response to specific physical triggers acting on the skin. A detailed history and provocation tests are the two key elements of the diagnostic workup, and threshold tests should be performed whenever possible. The underlying causes of physical urticarias are, as of yet, unknown. Trigger avoidance and symptom prevention by antihistamines and other drugs are the cornerstones of therapy. Physical urticaria can be severely disabling and detrimental to the quality of life of patients. Therefore, future research efforts should focus on the identification and characterization of relevant causes and mast cell-activating signals, as this could help to develop better treatment options.

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- Of importance
- Of major importance

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